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Mono-nitration of aromatic compounds via their nitric acid salts

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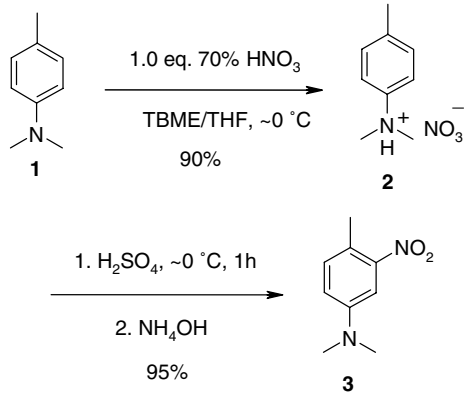
Abstract—Aromatic compounds bearing a basic nitrogen atom can be converted to the corresponding nitric acid salts. Mono-nitration of the compounds can be carried out by adding a dichloromethane solution of the salts to sulfuric acid, or by adding acetyl chloride (or trifluoroacetic anhydride) to a dichloromethane solution of the salts. This protocol provides, among other benefits, the most convenient and reliable way for the prevention of over-/under-nitration and is especially suitable for scale-up.

Nitration of aromatic nuclei is one of the most basic reactions in organic synthesis and is widely used in the pharmaceutical and chemical industries.[1] However, this reaction is notorious for several reasons, such as safety concerns, over-nitration, formation of regioisomers, and generation of impurities due to oxidation. These shortcomings are amplified when a nitration process is scaled up for commercial manufacturing, where process safety becomes paramount, precise charge of reagents cannot be easily achieved, dosing large amount of solids to a reactor could be technically challenging, the use of flash column chromatography to remove process impurities becomes impractical, and the disposal of large amounts of process wastes becomes an environmental issue and adds to financial cost. On the other hand, these challenges are the driving forces for the continuing research on the reaction that has created a large library of nitration reagents and methods.[2] While the creation of new reagents is important to achieve better results, the invention of novel process protocols can be equally effective in resolving critical nitration issues. In the previous paper[3] we disclosed a process for the synthesis of 4-(4-methoxy-3-nitrophenyl)morpholine via nitration of isolated nitric acid salt of 4-(4-methoxyphenyl)morpholine. This approach not only helped us to overcome a tough technical difficulty of preventing under-/over-nitration during manufacturing, but also resulted in the improvement of process safety, 59% increase of overall yield, 30% increase of capacity, and 40% decrease of total process wastes, among other benefits. Here we report that this protocol can be applied to a variety of aromatic substrates that contain one basic nitrogen atom in the molecule.



The essential of the protocol is exemplified in the scheme. *N*,*N*-dimethyl-*p*-toluidine (**1**) was converted to its nitric acid salt, **2**, by reacting with 1.0 equiv of nitric acid. The salt, precipitated out from solution during acid addition, was collected and dried. The nitration was effected by adding a dichloromethane solution of the salt to concentrated sulfuric acid. Table 1 lists some examples of arylamines. Good to excellent overall yield was observed in all the examples. The method applies to tertiary, secondary, and primary amines. Under the reaction conditions the protonated amino groups acted as deactivating groups, and thus activating groups on the aromatic rings dictated the regioselectivity. In the cases where there were no other groups (entries 3 and 9) the reactions produced mixtures of *meta*- and *para*-isomers. These results are similar to those observed when conventional methods were used.[4,6]

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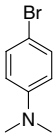
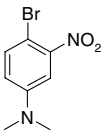
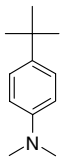
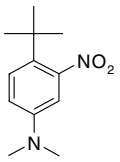
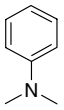
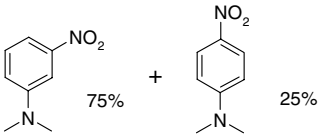
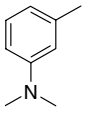
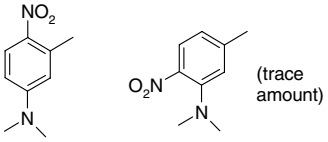
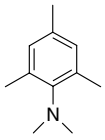
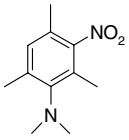
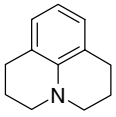
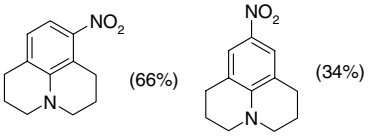
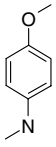
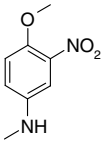
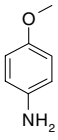
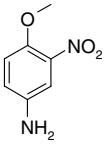
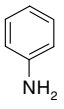
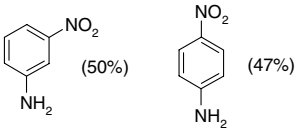
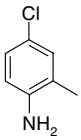
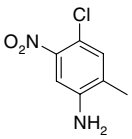
Table 1. Mono-nitration of arylamines

Entry	Substrate	Product[a]	Yield[b,c] (%)
1			94
2			94
3			93 (94[4])
4			93
5			84
6			95
7			92
8			88 (72[5])
9			93 (72[6])
10			92 (50[7])

[a] Isomeric ratio was estimated using ^{1}H NMR spectra of the crude products.
[b] Isolated yield.
[c] Yields in parentheses are the best isolated yield in the literature for the nitration of the same substrates in sulfuric acid.

The method can also be applied to other substrates with an aromatic nucleus and a nitrogen atom that is basic enough to form a salt with nitric acid. Table 2 lists some aromatic amines in which the amino groups are separated from the aromatic rings. Table 3 lists some examples of substrates with a basic nitrogen atom in a heterocyclic ring. Again good to excellent yield was observed in all the cases.

Nitration of the salts can also be catalyzed by other acids, often giving different regioselectivity. This is again illustrated by the nitration of **2**. Some examples are listed in Table 4. Acetic acid was not strong enough to initiate the reaction. But in trifluoroacetic acid (TFA) the reaction was completed within 1 h, producing *N*,*N*-dimethyl-2-nitro-*p*-toluidine (**4**) in 94% yield. When a solution of **2** in dichloromethane was added to a mixture of methanesulfonic acid (MsOH) in dichloromethane at 0 °C the nitration completed within 4 h and a mixture of **3** (7%) and **4** (93%) was isolated in 92% yield. At 17 °C the reaction was completed in 1 h and the ratio of **3**–**4** was changed to 2:98. When solid **2** was added to pure MsOH at 17 °C the reaction produced a mixture of **3** and **4** with a ratio of 25:75 in 91% yield. Also indicated in the table is that the nitration can be activated with acetyl chloride and trifluoroacetic anhydride. In both cases, **4** was isolated as the only product in good yield. When acetic anhydride was used no reactions occurred until the mixture was heated to 40 °C and the product contained multiple components. Similar results were observed when methanesulfonic anhydride (Ms_2O) was used.

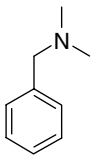
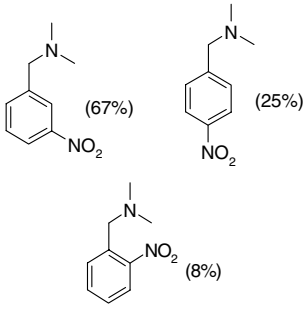
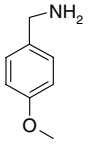
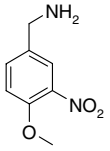
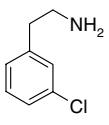
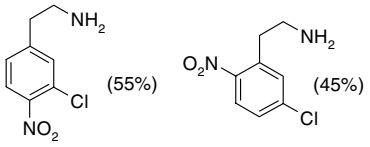
Despite the availability of a large variety of nitrating reagents (mostly various types of nitrate salts[8]) nitric acid/sulfuric acid mixture remains to be the top choice for commercial scale nitration processes. It is well accepted that the actual nitrating agent is nitronium ion and the concentration of the ion in the reaction mixture is a major factor to affect the reaction rate and the quality of the product. Many practical methods have been adopted to improve the nitration reaction based on the assumption of the equilibrium below:

$$HNO_3 + H_2SO_4 = H_2O + NO_2^+ + HSO_4^-$$

These methods include using fuming nitric acid, using large excess of concentrated sulfuric acid, and adding water scavengers to remove water in the reaction mixture. The use of isolated and dried nitric acid salt of a substrate automatically eliminates the part of water that would be brought to the reaction mixture if 70% HNO_3 is used and makes it possible to reduce sulfuric acid charge. This was well demonstrated in our process for the synthesis of 4-(4-methoxy-3-nitrophenyl)morpholine, in which we were able to reduce the sulfuric acid charge by 60% while still maintained the same reaction rate and product purity.[3]

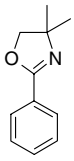
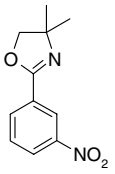
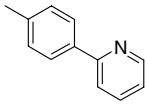
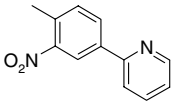
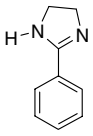
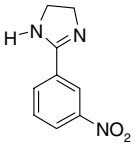
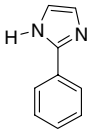
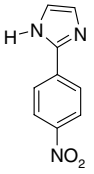
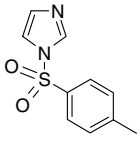
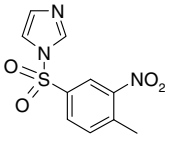
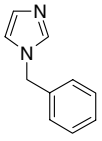
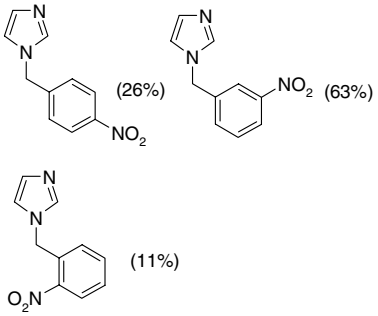
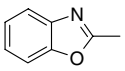
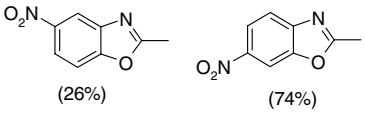
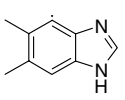
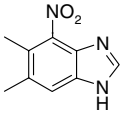
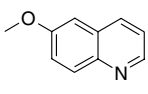
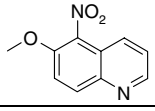
The use of isolated nitric acid salts provides an easy and reliable method to introduce a substrate and nitric acid into a reaction mixture in a 1:1 molar ratio, and thus over-/under-nitration could be effectively prevented and cleaner nitration could be expected. A typical conventional nitration process involves either the addition of substrates to concentrated sulfuric acid followed by the addition of a mixture of nitric acid and sulfuric acid, or the addition of substrates to a mixture of nitric acid and sulfuric acid. These operations are highly exothermic

Table 2. Mono-nitration of aromatic amines with the amino groups separated from the aromatic nuclei

Entry	Substrate	Product[a]	Yield[b] (%)
1			95
2			89
3			89

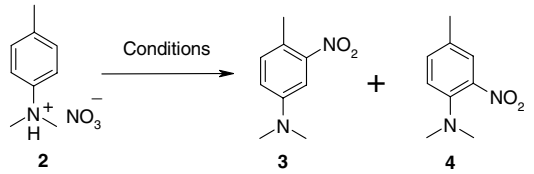
[a] Isomeric ratio was estimated using ^1H NMR spectra of the crude products.
[b] Isolated yield.

Table 3. Mono-nitration of aromatics containing a heterocyclic ring

Entry	Substrate	Product[a]	Yield[b] (%)
1			89
2			95
3			82
4			95
5			82
6			85
7			89
8			97
9			85

[a] Isomeric ratio was estimated using ^{1}H NMR spectra of the crude products.
[b] Isolated yield.

Table 4. Different conditions to carry out nitration



Entry	Reagent	Conditions	Product[a]	Yield[b] (%)
1	AcOH	60 °C, 4 h	No reaction	
2	TFA	0 °C, 1 h	**4**	94
3	MsOH[c]	0 °C, 4 h	**4** (93%) + **3** (7%)	92
4	MsOH[c]	17 °C, 4 h	**4** (98%) + **3** (2%)	93
5[d]	MsOH	17 °C, 1 h	**4** (75%) + **3** (25%)	91
6	AcCl	0 °C, 2 h	**4**	93
7	Ac_2O	40 °C, 16 h	Complicated mixture	
8	$(CF_3CO)_2O$	0 °C, 16 h	**4**	89
9	Ms_2O	20 °C, 4 h	Complicated mixture	

[a] Isomeric ratio was estimated using ^1H NMR spectra of the crude products.
[b] Isolated yield.
[c] 1:1 (v/v) mixture with CH_2Cl_2.
[d] Add solid **2** to pure MsOH.

and cause locally overheating in the reaction mixture that is not only a major safety concern but also a primary cause for side reactions. In our protocol the nitration process can be easily controlled by adjusting the addition rate of dichloromethane solution of the salts, and thus those shortcomings can be overcome. This may explain the high yields observed in all the examples in this Letter, especially the significantly higher yields for aniline and its derivatives (Table 1, entries 8–10).

The nitration of 4-substituted arylamines can be controlled at either *ortho* or *meta* positions. Typically, in sulfuric acid the *meta*-nitration predominates. *ortho*-Nitration can be achieved in less acidic media, such as $NaNO_2$/AcOH,[9] HNO_3/Ac_2O,[10] and $Tl(NO_3)_3$/MeCN.[11] It is believed that under these conditions the free base amino groups dictate the regioselectivity. This is consistent with our observations. For instance, the nitration of **2** in sulfuric acid afforded only **3** while in TFA, AcCl, and $(CF_3CO)_2O$ **4** was the only isolated product.[12] Thus, we provide here a method for the convenient control of regioselectivity for properly substituted arylamines.

Typical experimental procedures

Preparation of **2**: To a solution of 10 g (74 mmol) *N*,*N*-dimethyl-*p*-toluidine in a mixed solvent of 50 mL *t*-butyl methyl ether (TBME) and 50 mL THF at 0 °C was slowly added 6.6 g (74 mmol) of 70% nitric acid. After the addition the mixture was stirred for 1 h. The solid was filtered, washed with TBME, and dried at 20 °C under house vacuum overnight to give 13.6 g (90% yield) of **2**.

Preparation of **3**: A solution of 5 g (25.2 mmol) of **2** in 40 mL dichloromethane was slowly added to 20 g concentrated sulfuric acid while maintaining batch temperature at 0 ± 5 °C. After the addition the mixture was stirred for 1 h. The mixture was slowly added to 40 mL of cold water and was then basified with 28% NH_4OH solution until pH 10. The mixture was extracted with dichloromethane. The organic solution was dried over $MgSO_4$, filtered, and concentrated to give crude product, which was purified with flash column chromatography (silica gel, eluting with 1:1 CH_2Cl_2/hexane) to afford 4.3 g (95%) of **3**.

Preparation of **4**: To a solution of 5 g (25.2 mmol) of **2** in 25 mL dichloromethane was slowly added 4 g (50.4 mmol) acetyl chloride while maintaining batch temperature at 0 ± 5 °C. After the addition the mixture was stirred for 2 h. The reaction mixture was basified to pH 10 by the slow addition of 28% NH_4OH solution. The organic layer was separated and the aqueous layer was extracted with dichloromethane. The combined organic solution was washed with brine, dried over $MgSO_4$, filtered and concentrated to give a crude product, which was purified with flash column chromatography (silica gel, eluting with 1:1 CH_2Cl_2/hexane) to afford 4.3 g (93% yield) of **4**.

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12. For a detailed discussion of regioselectivity, please see Ref. 3.